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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,046	02/01/2001	Johannes Eduard Maria Antonius Debets	DX01073K	3164

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EXAMINER	
ANDRES, JANET L	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/775,046	Applicant(s) ANTONIUS DEBETS ET AL.	
	Examiner Janet L Andres	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 12-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II and species election of interleukin-1 ϵ antagonists, inflammation, and co-administered chemokine receptor antagonist in Paper No. 12 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden to search effects on proliferation and tissue remodeling as well as inflammation or to search administration of interleukin-1 antagonists alone as well as with chemokine receptor antagonists. Applicant states that proliferation and tissue remodeling are each part of the inflammatory process on p. 3 of the response filed 11 December 2002. Applicant's arguments with respect to the consequences of inflammation are found persuasive and this basis of the species election is withdrawn. Applicant's argument that a search for administration of IL-1ϵ antagonists alone as well as with a chemokine antagonist would not constitute a burden is also found persuasive and this basis of the species election is also withdrawn. The Examiner notes, however, that the co-administration is with an antibody to IL-R6, not an IL-1ϵ antagonist. No errors in the restriction requirement or the requirement for election of interleukin species were provided and thus the election of Group II and of interleukin-1ϵ are treated as election without traverse; see MPEP §818.03(a). The restriction requirement is made final. Claims 4-11 as they pertain to antagonists of interleukin-1ϵ and of IL-1R6 and modulation of inflammation are thus under examination in this application. Claims 1-3 and 12-20 are withdrawn from consideration as being drawn to a non-elected invention.

Specification

2. The disclosure is objected to because of the following informalities: Not all of the sequences in figure 1 have been given sequence identifying numbers in the brief description of the drawings on p. 4, lines 9-14. See MPEP §2422. Also, on p. 77, line 34, "IL-" presumably refers to an IL-1 receptor but the rest of the receptor designation has been omitted.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 4-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman,* (230 USPQ 546 (Bd Pat. App. & Int. 1986)); *In re Wands,* 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

These claims, as examined in light of the species election, are drawn to methods of using an inhibitor of interleukin-1ϵ (claims 4-7) or an inhibitor of IL-1R6 (claims 8-11) to inhibit

inflammation and processes resulting from inflammation. Applicant teaches on p. 73, lines 27-39, p. 77, lines 22-24, and p. 94, lines 31-33, that IL-1ε activates NFκB via IL-1R6. However, no teachings are provided that would allow one of skill in the art to predict that this activation would be pro-inflammatory, and thus that inhibition of such an effect could be used to treat inflammation. There is no guidance as to the physiological results of IL-1R6 activation; the experiments were done in transfected cells that do not normally bear the receptor (p. 77, lines 31-34, p. 78, lines 1-2). No nexus is provided between IL-R6 function and inflammation and one of skill in the art would not, absent such guidance, be able to predict that such a nexus exists. This receptor, which Applicant indicates on p. 11, line 7, is also known as IL-1Rrp-2, is found in lung, epididymis, testis, and the cerebral cortex (Lovenberg et al., J. Neuroimmunol. 1996, vol. 70, no. 2, pp. 113-122), not in cells associated with the immune system. Thus the skilled artisan would not be able to predict what the results of antagonizing its function, either by inhibiting IL-1ε or by inhibiting it directly, would be. That IL-1ε is upregulated in response to IL-1β and TNFα, as stated by Applicant on p. 12, lines 1-3, provides no guidance as to its function; Applicant states that IL-1δ is also upregulated, yet has the opposite function (p. 11, line 34, p. 73, lines 30-33). Similarly, that IL-1δ, IL-1ε, and IL-R6 are upregulated in psoriasis (p. 79, lines 4-8) provides no information as to what their physiological roles might be.

Additionally, the art describes the molecule referred to by Applicant as IL-1ε as an interleukin-1 receptor antagonist. WO 99/36541 (Marshall et al., 1999) teaches that IL-1ra β, which is identical to Applicant's SEQ ID NO: 4, which Applicant identifies as human IL-1ε, can be used to treat inflammation on p. 3, lines 12-16. EP 855404 (Young, 1998) similarly teaches that this polypeptide is an IL-1 receptor antagonist that can be used to treat inflammation on p. 3,

lines 5-9. U.S. patents 6,054,559 (Young, 2000) and U.S. patent 5,863,769 (Young, 1999) also identify this molecule as an IL-1 receptor antagonist (see column 2, lines 49-64 of the '559 patent and column 2, lines 36-45 of the '769 patent). While none of these documents provide working examples or other objective evidence of this molecule's function, its identification as an IL-1 receptor antagonist and the teachings of each that an IL-1 receptor antagonist inhibits interleukin 1 function would indicate to one of skill in the art, absent evidence to the contrary, that IL-1ϵ would antagonize interleukin-1 function and thus itself be anti-inflammatory. Thus, based on the teachings of the prior art, one of skill would expect that inhibition of this molecule would have pro-inflammatory effects. Applicant's specification does not provide sufficient guidance to indicate that the opposite would predictably occur. Applicant states only that IL-1ϵ did not activate other receptors; there is no guidance as to whether it would function as an inhibitor of such receptors as indicated by references cited above, and thus itself be an anti-inflammatory agent, the inhibition of which would have the opposite effect of that claimed by Applicant. Only results for IL-1δ are taught (p. 74, lines 1-4).

Claims 4, 5, 7-9, and 11 encompass antagonists other than antibodies or muteins. While one of skill in the art might be able to generate antagonistic muteins and antibodies to IL-1ϵ and IL-R6 without undue experimentation, the specification provides no guidance as to what other molecules could be used as inhibitors. No structural or other characteristics of such inhibitors are provided and thus one of skill would not predictably be able to generate them.

Claim 6 is drawn to a method in which the response is in Th2, not Th1 cells. Since, as stated above, one of skill in the art would not predict that an anti-inflammatory effect could be achieved, the cells that would be affected are also not predictable. Further, the effect is

dependent on receptor expression. Applicant teaches on p. 79, lines 1-3, that IL-R6 is expressed on monocytes, keratinocytes, and fibroblasts. None of these is a Th2 cell; one of skill would thus not predict that they could be affected via the IL-1R6 receptor as required by claim 6. Lovenberg et al. indicates on p. 118 that IL-1R6 was not detected in any cell lines and thus fails to provide compensatory teachings.

Claims 10 and 11 are drawn to coadministration of an IL-1R6 antagonist and a chemokine receptor antagonist. The art teaches that chemokine receptor antagonists function as anti-inflammatory agents. See, for example, McColl and Lewis, J. Immunol. 1999, vol. 163(5), pages 2829-2835, which teaches that inhibition of CXCR2 is anti-inflammatory. However, one of skill in the art would not be able to predict, based on such teachings, that the combination of a chemokine receptor inhibitor and an inhibitor of IL-1R6 would have the same effect, since the effects of an IL-1R6 antagonist are not themselves predictable for the reasons set forth above.

Thus, since Applicant has not provided sufficient guidance as to what cell types express the receptor, what the results of receptor activation would be, or as to what other effects the IL-1ϵ might have, and since the art teaches that IL-1ϵ is in fact a receptor antagonist, one of skill in the art would not be able to predict that inhibition of IL-1ϵ would inhibit inflammation. Without further guidance predictive of a successful outcome, it would require undue experimentation for one of skill in the art to practice Applicant's invention.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 5 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

These claims require that an effect not involve endothelial cells (claim 5) or Th1 cells (claim 6). The negative limitation is a limitiaton on the mechanism with no corresponding method step to achieve that outcome.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Andres, Ph.D., whose telephone number is (703) 305-0557. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564. The fax phone number for this group is (703) 872-9306 or (703) 872-9307 for after final communications.

Communications via internet mail regarding this application, other than those under U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[yvonne.eyler@uspto.gov]**.

All Internet email communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly

set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet Andres, Ph.D.
Patent Examiner

March 9, 2003